Persistent Diarrhea, Arthritis, and Other Complications of Enteric Infections: A Pilot Survey Based on California FoodNet Surveillance, 1998–1999

Judy R. Rees,[1,2,a] Mary Ann Pannier,[1] Alexander McNees,[1] Sue Shallow,[1] Frederick J. Angulo,[4] and Duc J. Vugia[3]

[1]California Emerging Infections Program, Oakland, [2]School of Public Health, University of California, Berkeley, [3]California Department of Health Services, Berkeley, California; [4]Centers for Disease Control and Prevention, Atlanta, Georgia

Numerous complications of enteric infections have been described, including persistent diarrhea, reactive arthritis, and Guillain-Barré syndrome. We determined the frequency of self-reported complications of enteric infections in a pilot study in the California site of the Foodborne Diseases Active Surveillance Network. From 1 April 1998 through 31 March 1999, active surveillance identified 1454 infections in Alameda and San Francisco counties, of which 52% were *Campylobacter* infections, 22% were *Salmonella* infections, 15% were *Shigella* infections, 6% were *Cryptosporidium* infections, 2% were *Escherichia coli* O157:H7 infections, 2% were *Yersinia* infections, and 1% were *Vibrio* infections. We mailed surveys to 1331 eligible participants, and 571 (43%) were returned. A new health problem following infection was reported by 153 (27%) of the respondents: 12 (8%) reported new onset of joint pain and 53 (35%) reported new gastrointestinal symptoms, of whom 38 reported persistent diarrhea, including 2 who reported irritable bowel syndrome. Three respondents reported hair loss. The frequency, nature, and etiology of these complications merit further investigation.

Many complications of enteric infections have been described, including persistent diarrhea, reactive arthritis, Reiter syndrome, inflammatory bowel disease, autoimmune thyroid disease, hemolytic uremic syndrome, and Guillain-Barré syndrome [1, 2]. It has been estimated that 2%–3% of cases of foodborne infections lead to chronic illness [1]. Because an estimated 76 million episodes of food-related illnesses occur annually [2], many people are at risk of developing chronic symptoms following foodborne diseases. However, the frequency of such chronic complications of enteric infections has not yet been evaluated at a population-based level. Our aim in this pilot study was to stimulate further research into the impact of enteric infections by identifying the possible range of their complications in a population-based cohort of persons with laboratory-confirmed enteric infections.

METHODS

The Foodborne Diseases Active Surveillance Network (FoodNet) conducts population-based active surveillance for laboratory-confirmed infections with enteric pathogens including *Escherichia coli* O157:H7 and *Campylobacter, Salmonella, Shigella, Yersinia, Vibrio,* and *Cryptosporidium* species [3]. We collected data from all cases in which one of these pathogens was isolated from samples of any body fluid or tissue except urine. In the California FoodNet site, all clinical laboratories in Alameda and San Francisco counties that process samples for detection of enteric pathogens were contacted at least weekly to ascertain the results for

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[a] Present affiliation: Department of Community and Family Medicine, Center for Environmental Health Sciences, and Norris Cotton Cancer Center, Dartmouth Medical School, Lebanon, New Hampshire.

Reprints or correspondence: Dr. Judy Rees, Biostatistics and Epidemiology, Dartmouth Medical School, HB 7927, Dartmouth-Hitchcock Medical Center, One Medical Center Dr., Lebanon, NH 03756 (judith.rees@dartmouth.edu).

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Table 1. Laboratory-confirmed enteric infections and self-reported new symptoms following enteric infection for 1454 study participants.

	No. (%) of study participants					
Pathogen genus	With laboratory-confirmed infection	To whom survey was mailed[a]	Who completed survey	With persistent GI symptoms[b]	With rheumatologic symptoms[b]	With hair loss
Campylobacter	757 (52.1)	706 (93.2)	324 (45.9)	28 (8.6)	9 (2.8)	1 (0.3)
Salmonella	326 (22.4)	271 (83.1)	100 (36.9)	8 (8.0)	2 (2.0)	2 (2.0)
Shigella	213 (14.6)	201 (94.4)	81 (40.3)	5 (6.2)	1 (1.2)	0
Cryptosporidium	87 (6.0)	85 (97.7)	35 (41.2)	10 (28.6)	0	0
Escherichia coli O157:H7	35 (2.4)	34 (97.1)	22 (64.7)	0	1 (4.5)	0
Yersinia	26 (1.8)	26 (1000)	8 (30.8)	2 (25.0)	0	0
Vibrio	10 (0.7)	8 (80.0)	1 (12.5)	0	0	0
Total	1454 (100.0)	1331 (91.5)	571 (42.9)	53 (9.3)	12 (2.1)	3 (0.5)

[a] Excludes individuals with no known address and those known to have died. Includes 55 surveys that were returned by the US Postal Service as "undeliverable." The overall response rate for the 1276 participants assumed to have received the survey was 45%.
[b] Expressed as percentage of respondents who completed the survey.

laboratory-confirmed cases; laboratories outside these counties that commonly test for *Cryptosporidium* in specimens from residents of the 2 counties were also contacted. The 1998 population of the 2 counties, according to the postcensus estimate, was 2.2 million persons [4]. All persons with a laboratory-confirmed infection with *Campylobacter, Salmonella, Shigella, Yersinia, Vibrio,* or *Cryptosporidium* species or *E. coli* O157:H7 from whom the specimen had been obtained during the period 1 April 1998 through 31 March 1999 were eligible for the study. We obtained informed consent from participants and conducted this study in accordance with guidelines for human research as specified by the US Department of Health and Human Services.

We conducted a survey of persons who (1) had a laboratory-confirmed infection with one of the listed organisms during the study period, (2) were residents of San Francisco or Alameda counties and had a known mailing address, and (3) were not known to be dead at the time the surveys were mailed. Three months after laboratory confirmation of their enteric infection, we mailed eligible participants a short questionnaire requesting information about any health problems they had before their infection and any new health problems that had developed since the infection (see Appendix). Participants were specifically asked about diarrhea and arthritis, including the date of onset and nature of the symptoms, any diagnosis or treatment they had been given, and the approximate duration of the problem, if symptoms were no longer present. We identified a subset of 371 nonrespondents with a positive culture result obtained during the period September 1998 through February 1999 and sent them a second, identical questionnaire during December 1999 and January 2000 (i.e., 10–15 months after diagnosis). We then requested further information by telephone from all participants who reported having had new symptoms since their laboratory-confirmed infection, and we reviewed medical records, if appropriate.

RESULTS

From 1 April 1998 through 31 March 1999, we identified 1454 residents of Alameda and San Francisco Counties as having a laboratory-confirmed enteric infection: 757 with *Campylobacter* infection (34.4 cases/100,000 population); 326 with *Salmonella* infection (14.8 cases/100,000 population); 213 with *Shigella* infection (9.7 cases/100,000 population); 87 with *Cryptosporidium* infection (4.0 cases/100,000 population); 35 with *E. coli* O157:H7 infection (1.6 cases/100,000 population); 26 with *Yersinia* infection (1.2 cases/100,000 population); and 10 with *Vibrio* infection (0.5 cases/100,000 population) (table 1). Although the laboratory confirmation for 1441 (99%) of the 1454 cases was from a stool specimen, 42 patients also had a positive blood culture result.

Of the 1454 patients with a laboratory-confirmed enteric infection, 6 were known to have died within 1 week after the specimen collection date (according to hospital records), and a mailing address was not available for 117 patients. After excluding these 123 patients, we mailed questionnaires to the remaining 1331. Fifty-five questionnaires were returned as undeliverable by the US Postal Service, leaving 1276 questionnaires that we assumed were delivered successfully. Of these 1276, a total of 571 (45%) were completed and returned. There were some differences between the characteristics of respondents and those of nonrespondents: overall, the distributions of infecting organisms differed significantly between respondents and nonrespondents ($P = .005$; χ^2 test, 6 df), and the

Table 2. Summary of history and symptoms for 12 (8%) of 571 respondents who reported new joint pain symptoms following enteric infection.

Patient	Age in years, sex	Relevant medical history	New symptoms reported	Patient response and/or medical findings, and outcome
1	24, M	…	Unilateral knee stiffness 3 months after *Campylobacter* infection was diagnosed	Did not seek medical attention; symptoms persisted for at least 1 month
2	29, F	Intermittent bilateral knee pain	Increased knee pain and stiffness soon after *Campylobacter* infection was diagnosed	Did not seek medical attention; symptoms persisted for at least 4 months
3	42, F	…	Bilateral knee pain and swelling, which worsened with exercise, 1 month after *Campylobacter* infection was diagnosed	Did not seek medical attention; symptoms persisted for at least 5 months
4	42, M	Mild psoriasis	Fever 8 weeks after *Campylobacter* infection was diagnosed; generalized myalgia and arthralgia present	Investigated for unexplained anemia and abnormal liver function test results; symptoms and test results normalized 3 weeks later
5	44, F	*Escherichia coli* O157:H7 infection 5 months previously	Bilateral pain in the joints of the hands and feet soon after *Campylobacter* infection was diagnosed	Diagnosed with ulcerative colitis during this episode; joint pains continue to recur, with flares of colitis
6	51, F	…	Pain and swelling in the 5th finger of the left hand 4 months after *Campylobacter* infection was diagnosed	Did not seek medical attention; symptoms resolved 3 months later
7	61, M	…	Pain in the joints of the right hand 2 months after *Campylobacter* infection was diagnosed	Did not seek medical attention; symptoms persisted for at least 2 months
8	68, F	Osteoarthritis for 10–15 years	Unilateral hip and back pain 4 weeks after *Campylobacter* infection was diagnosed	Was told condition was "possible sciatica"; symptoms persisted for at least 7 months
9	72, F	…	Bilateral finger, hand, and wrist pain 3 months after *Campylobacter* infection was diagnosed	Did not seek medical attention; symptoms persisted for at least 3 months
10	46, M	Ulcerative colitis and corticosteroid use	Pain in both hips, the right knee, and the left thumb soon after *Salmonella* infection was diagnosed	Found to have avascular necrosis of the hip related to steroids; was told thumb condition was arthritis; symptoms persisted for at least 4 months
11	53, M	…	Pain in the right index finger, which had no history of injury, 1 month after *Salmonella* infection was diagnosed	Was told condition was "possible damaged tendon"; symptoms persisted for at least 8 months
12	36, F	…	"Arthritis" beginning 2 months after *Shigella* infection was diagnosed	Subject could not be located for further follow-up

NOTE. All participants were white and non-Hispanic except patient 11, who was white and of unknown ethnicity.

response rate was highest among persons infected with *E.coli* O157:H7 (22 [65%] of 34 persons). Of the 994 of participants (78%) whose race or ethnicity was known, the characteristics of respondents and nonrespondents differed significantly ($P < .001$; χ^2 test, 6 df). Sixty percent of respondents and 42% of nonrespondents were white, whereas 4% of respondents and 11% of nonrespondents were African American. Respondents were also older than nonrespondents (32 vs. 29 years; $P = .004$), and the proportion of males was slightly lower among respondents than among nonrespondents (54% vs. 59%; $P = .083$).

Of the 571 respondents, 153 (27%) reported new symptoms following their enteric infections. Of those respondents with new symptoms, 53 (35%) reported new gastrointestinal symptoms following their enteric infection. The most frequent symptom, reported by 46 respondents with new gastrointestinal symptoms, was an alteration in bowel habits for at least 3 months after the diagnosis of enteric infection. Thirty-eight of those 46 reported persistent diarrhea of at least 3 months' duration (diarrhea was defined as ⩾3 loose stools in a 24-h period) (table 2). Altered bowel habits were reported by 10 (11.5%) of 87 persons with *Cryptosporidium* infection, 2 (7.7%) of 26 with *Yersinia* infection, 23 (4.1%) of 757 with *Campylobacter* infection, 7 (2.1%) of 326 with *Salmonella* infection, and 4 (1.9%) of 213 with *Shigella* infection. Of the participants who reported altered bowel habits, 2 noted that they had been diagnosed with irritable bowel syndrome following *Salmonella* infection and *Campylobacter* infection (1 each).

Of the 153 respondents with new symptoms, 12 (8%) reported new joint pains that had not been present before the enteric infection (table 2). The age of these 12 respondents ranged from 26 to 72 years. Their symptoms ranged from mild monoarticular pain to moderate pain and swelling in >1 joint sufficient to disrupt their usual activities. Seven of the 12 re-

spondents with new joint pain did not consult a health care provider about the new joint pain, and information about their symptoms was imprecise. However, 10 of the 12 participants reported that the new rheumatic problems had lasted at least 4 months, and 6 had ongoing symptoms at the time they were interviewed by telephone. Joint pain was reported by 9 (1.2%) of 757 patients with *Campylobacter* infection, 2 (0.6%) of 326 with *Salmonella* infection, and 1 (0.5%) of 213 with *Shigella* infection.

Three female respondents reported hair loss within 2–3 weeks after the diagnosis of enteric infection. Two reported partial hair loss within several weeks after diagnosis of infection with *Salmonella* serotype Typhi, although the hair of the only respondent for whom this information was known grew back. Both women had taken ciprofloxacin, and one had also taken ceftriaxone. These were 2 of 17 patients confirmed as having *S.* Typhi infection. In addition, reversible but complete loss of hair on the scalp was reported in a 2-year-old girl following *Campylobacter* infection for which she had not received antibiotic therapy.

A variety of other symptoms were reported by respondents: however, most resolved within 4 months after the laboratory-confirmed diagnosis of enteric infection. Examples include herpes zoster reported by a patient after *Campylobacter* infection and herpes simplex ulceration of the mouth reported by a patient after infection with *E. coli* O157:H7.

DISCUSSION

In this pilot study, we identified a range of self-reported symptoms that might be attributable to gastrointestinal infection: persistent diarrhea, a variety of new rheumatologic symptoms, the development of irritable bowel syndrome, and hair loss. In previous reports, persistent diarrhea was the most common complication of bacterial enteric infections, as it was in our study. McKendrick and Read [5] reported persistent bowel dysfunction in 32% of 38 participants 1 year after *Salmonella* infection. Another survey of 544 participants with microbiologically proven bacterial enteritis showed that 90 respondents (25% of respondents; 16.5% of participants) still had altered bowel habits 6 months after their original illness [6]. The results of that study, which focused specifically on the gastrointestinal effects of enteric infection, showed that 7% of participants with enteric infection had developed new symptoms that fulfilled the modified Rome criteria for irritable bowel syndrome [7]. In our study, a persistent alteration in bowel habits was the most commonly reported new symptom 3 months after diagnosis of an enteric infection. This suggests that an important possibility for future study would be systematic assessment of the prevalence of gastrointestinal dysfunction and irritable bowel syndrome among participants one to several years after an enteric infection, as well as the possible role of antibiotic therapy in the development or prevention of these symptoms.

The incidence of new joint pain following enteric infection in our study is consistent with that in previous reports that have suggested that 1%–4% of adults with *Campylobacter, Salmonella,* or *Shigella* infections subsequently develop reactive arthritis [8]. We found that 0.5%–1.2% of persons with laboratory-confirmed *Shigella, Salmonella,* or *Campylobacter* infections reported new onset of joint pain following their infection. *E. coli* strains, *Klebsiella pneumoniae,* and *Yersinia* species have also been suspected of causing reactive arthritis [1, 9], but we did not identify any such cases in the present study. Of the rheumatologic syndromes, ankylosing spondylitis, reactive arthritis, and Reiter syndrome appear to be more likely and more severe in patients with major histocompatibility class antigens B27 and B7 [10–13]. The onset of reactive arthritis tends to occur relatively soon after infection, and the course may be prolonged. In one series, the mean interval between the onset of *Campylobacter jejuni* enteritis and Reiter syndrome or reactive arthritis was 10 days [8]. Following an outbreak of *Shigella* infection aboard a US Navy cruiser, 10 sailors developed Reiter syndrome within 2 weeks, and 4 of 5 who were traced 14 years later were found to have chronic disease [14]. Although the participants in our study reported a variety of rheumatologic symptoms, a diagnosis could not easily be confirmed by a mailed survey with only telephone follow-up. Most of the participants had not sought medical attention, and it is unclear whether they would eventually have done so. Clinical and laboratory investigations of such cases and long-term follow-up studies of infected patients would be of interest, as would studies of the role of antibiotic therapy and genetic factors in the etiology of these syndromes. One experimental study showed that reactive arthritis triggered by *Yersinia* infection in rats was completely prevented by early administration of ciprofloxacin [15].

Hair loss is an uncommonly reported complication of typhoid fever. Haefeli et al. [16] describe a series of reports of hair loss among patients with pyrexial illnesses (including typhoid fever) during the preantibiotic era, as well as a series of 5 cases of reversible hair loss associated with a small outbreak of typhoid (5 patients) in Switzerland in the 1990s. All 5 patients with hair loss had been treated with ciprofloxacin, but the evidence suggested that the hair loss had an infectious rather than an iatrogenic etiology and perhaps was related to the high fevers involved. Of the 3 respondents in our present study who reported hair loss, 2 lost hair after having typhoid fever that had been treated with ciprofloxacin (and also, in 1 case, with ceftriaxone), and 1 lost hair after having an untreated *Campylobacter* infection. The maximum body temperatures recorded during the illnesses of these 3 respondents are not known.

Our methods had several limitations that should be addressed in future studies. The low response rate for the mailed questionnaire might be improved by using earlier and multiple mailings or by providing incentives for completing the survey. We found evidence that those who responded to the survey differed from those who did not respond with respect to race, sex, and the infecting organism. The mailed survey was a useful hypothesis-generating tool, but it was less useful in determining diagnoses and was not designed to evaluate a causal link between infection and new symptoms. That we found relatively few substantial new symptoms in our population suggests that follow-up data for a much larger population of infected patients would be needed to detect other possible but rarer complications. Furthermore, to investigate whether there was a significant association between these symptoms and any preceding infection, one would need to compare the incidence of symptoms among previously infected patients with the incidence in a control group. In the absence of such a control group, we could not determine whether the new symptoms reported by participants in our study were any more frequent than would be expected in an uninfected population. Thorough clinical investigations of participants with self-reported syndromes of interest will be necessary to address these limitations and to investigate etiologic hypotheses. Such investigations should include further questioning, laboratory tests, and the use of appropriate controls.

In this pilot study, we identified a variety of self-reported symptoms among people who had recently had enteric infections, the most common of which were persistent gastrointestinal symptoms and new rheumatologic symptoms. The possible association between enteric infections and a variety of chronic symptoms merits further investigation.

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APPENDIX

A. THESE QUESTIONS ARE ABOUT YOUR HEALTH BEFORE YOUR INFECTION IN (Month Year)?

1. What chronic illnesses do you have that were present **BEFORE (Month Year)**?

2. **BEFORE (Month Year)**, did you have a problem with chronic diarrhea?
(Diarrhea is 3 or more loose bowel movements in a 24 hour period)

YES ❒ **NO** ❒ ➨ skip to question 3

On how many days per week did you usually have diarrhea? _____

Approximately when did your diarrhea begin?_____

Have you seen a doctor or nurse about the diarrhea? **YES** ❒ **NO** ❒

What have you been told is the cause of the diarrhea?_____

3. **BEFORE (Month Year)**, did you have a problem with arthritis?
(Arthritis is pain, swelling and/or reduced movement in one or more joints)

YES ❒ **NO** ❒ ➨ skip to question 4

Approximately when did your arthritis begin?_____

Have you seen a doctor or nurse about the arthritis? **YES** ❒ **NO** ❒

What have you been told is the cause of the arthritis?_____

B. THESE QUESTIONS ARE ABOUT YOUR HEALTH SINCE YOUR INFECTION IN (Month Year).

4. **SINCE (Month Year),** have you had any other health problems? **YES** ❒ **NO** ❒ ➨ skip to question 5

If yes, please describe these problems in the chart below.

What new health problem have you had?	Did you see a doctor or nurse?	Approximately when did this problem begin? Month/Year	Do you still have this problem?	If the problem is gone, when did it end? (Month/Year)
	YES ❒ **NO** ❒		**YES** ❒ **NO** ❒	
	YES ❒ **NO** ❒		**YES** ❒ **NO** ❒	
	YES ❒ **NO** ❒		**YES** ❒ **NO** ❒	

5. **SINCE (Month Year)**, have you had persistent or recurrent diarrhea? (Diarrhea is 3 or more loose bowel movements in a 24 hour period)

YES ❒ **NO** ❒ ➨ skip to question 6

On how many days per week do you usually have diarrhea?_____

Have you seen a doctor or nurse about the diarrhea? **YES** ❒ **NO** ❒

What have you been told is the cause of the diarrhea?_____

Do you still have the diarrhea? **YES** ❒ **NO** ❒ If **NO**, when did it stop? Month/Year _____

6. **SINCE (Month Year),** have you had a problem with arthritis? (Arthritis is pain, swelling and/or reduced movement in one or more joints

YES ❒ **NO** ❒ ➨ skip to question 7

Approximately when did your arthritis begin?_____

Have you seen a doctor or nurse about the arthritis? **YES** ❒ **NO** ❒

What have you been told is the cause of the arthritis?_____

Do you still have the arthritis? **YES** ❒ **NO** ❒ If **NO**, when did it stop? Month/Year _____

7. Please check the correct boxes that describe your race and ethnicity.

RACE:

❒ African American ❒ American Indian/Alaskan Native ❒ Asian/Pacific Islander
❒ White ❒ Other (please specify)_____

ETHNICITY:

❒ Hispanic ❒ Non-Hispanic

8. Is there anything else about your health that you would like us to know?

Questionnaire used to collect data on symptoms associated with enteric infection

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